

Preface

The toxicology of phthalic acid ester (PAE) plasticizers, especially di(2-ethylhexyl) phthalate (DEHP), continues to be a topic of great concern because of their common use, likelihood of human exposure, and possibility of causing cancer and birth defects. An impressive array of scientists have periodically reviewed the state of knowledge of these agents in a series of international conferences beginning in 1972. The papers generated from these meetings have been published in *Environmental Health Perspectives*.

The initial conference (Environ. Health Perspect., 3, 1973) focused largely on production and use of PAEs, acute toxicity, interactions with blood, and environmental fate. Due to the lack of serious toxicity encountered at that time, PAEs were considered by many to be relatively innocuous to humans by anticipated modes of exposure. A later conference was convened in 1981 (Environ. Health Perspect., 45, 1982) to discuss the more recent evidence that chronic oral administration of DEHP caused hepatic neoplasms in rats and mice. This discovery of a serious consequence to long-term, high-level PAE exposure caused concern both for consumers and for users of DEHP-contaminated foods or materials, as well as for the carcinogenic potential of other PAEs. In addition, it became apparent at this conference that additional attention needed to be given to potential reproductive effects of PAEs.

The effects of PAEs on peroxisomes also became prominent at the 1981 conference. This organelle proliferates in hepatocytes in response to oral administration of certain PAEs and other compounds. Induced also by several lipid lowering drugs such as clofibrate, hepatic peroxisome proliferation in several species of experimental animals has been associated with the development of hepatic neoplasia. The possibility that peroxisome induction could increase the generation of reactive oxygen species in hepatocytes, overwhelming defense mechanisms and leading to tissue injury and neoplasia, and the relative potential for this speculative

sequence to occur in species such as man have become topics of intense debate.

The third conference, held in 1984, was convened in large part to answer questions arising from the 1981 meeting and to present the results of relevant new research on this subject in an international forum. The conference was held at the University of Surrey (Guildford), as a satellite to the Ninth International Congress of Pharmacology (London). Dr. James Bridges, Director of the Robens Institute for Industrial and Environmental Health and Safety, hosted the meeting at the University's conference facilities. Dr. John Thomas, conference organizer, welcomed the attendees and officiated.

As the toxic effects of PAEs were described at previous meetings, the major themes of this conference were mechanisms of toxicity, structure-activity relationships and cross-species extrapolations. Several papers addressed mechanisms of carcinogenicity (DNA binding, tumor promotion, peroxisome proliferation, mutagenesis/clastogenesis, and reproductive toxicity (testicular injury, teratogenicity). Others focused on PAE metabolism in various species and the potential significance to human risk estimation of species differences in PAE metabolism and biological effects. Overviews of various large scientific programs were also offered.

We can expect future discussions and debate on the meaning of much of this new research data relative to measures that need to be taken to protect workers and the general public from undue risks related to PAE exposures.

NOTE: "Hepatic effects of phthalate esters and related compounds—*in vivo* and *in vitro* correlations," by B. G. Lake, T. J. B. Gray, and S. D. Gangolli, which was presented at this conference, will be published in *Environmental Health Perspectives*, Volume 67.

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